UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/509,098	03/22/2000	MASAYUKI TSUCHIYA	053466/0274	7563

7590 04/29/2002

FOLEY & LARDNER
3000 K STREET NW
PO BOX 25696
WASHINGTON, DC 20007-8696

EXAMINER
HELMS, LARRY RONALD

ART UNIT	PAPER NUMBER
1642	12

DATE MAILED: 04/29/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/509,098	Applicant(s) TSUCHIYA, MASAYUKI	
	Examiner Larry R. Helms	Art Unit 1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 March 2002*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *3-14* is/are pending in the application.

4a) Of the above claim(s) *6-13* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *3-5 and 14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Claims 3-14 are pending.

Claims 1-2 have been canceled.

Claims 3 and 5 have been amended.

Claim 14 has been added.

Claims 3-5 and 14 are under examination

2. Claims 6-13 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention. Applicant timely traversed the restriction (election) requirement in Paper No. 7.

3. The text of those sections of Title 35 U.S.C. code not included in this office action can be foound in a prior Office Action

4. The following Office Action contains some NEW GROUNDS of rejection.

Rejections Withdrawn

5. The rejection of claims 1-5 under 35 U.S.C. 112, second paragraph, for parts a, c, d, e, f, and i in paragraph 6 of the previous Office Action as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in view of the amendments to the claims.

6. The rejection of claims under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter is withdrawn in view of the amendments to the claims.

7. The rejection of claims 3 and 5 under 35 U.S.C. 102(b) as being anticipated by Sato et al (Molecular Immunology 31:371-381, 1994, IDS #4) is withdrawn in view of the amendments to the claims.

8. The rejection of claims 3 and 5 under 35 U.S.C. 102(b) as being anticipated by Co et al (Proc. Natl. Acad. Sci. USA 88:2869-2873, 1991, IDS #4) is withdrawn in view of the amendments to the claims.

9. The rejection of claims 3 and 5 under 35 U.S.C. 102(b) as being anticipated by Roguska et al (Protein Engineering 9:895-904, 10/96, IDS #3) is withdrawn in view of the amendments to the claims.

10. The rejection of claims 3 and 5 under 35 U.S.C. 103(a) as being unpatentable over Sato et al (Molecular Immunology 31:371-381, 1994, IDS #4) and Co et al (PNAS 88:2869-2873, 1991, IDS #4) and Roguska et al (Protein Engineering 9:895-904, 1996, IDS #3) as applied to claims 1-3 and 5 above, and further in view of Queen et al (PNAS 86:10029-10033, 1989, IDS #4) is withdrawn in view of the New Grounds of rejection below.

Response to Arguments

11. The rejection of newly added claim 14 and claims 3-5 under 35 U.S.C. 112, second paragraph, for parts b, g, and h in paragraph 6 of the previous Office Action as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is maintained.

The response filed 3/18/02 has been carefully considured but is deemed not to be persuasive. The response states "artificial amino acid sequences...refer to those amino acid sequences that can not be found in nature... See page 12, lines 29-31" (see page 4 of response). In response to this argument, the specification describes "artificial amino acid sequences" not "artificial amino acids" which is recited in claims 3, 5, and 14. Again it is unclear what is meant by the phrase. Does it mean unnatural amino acids or mimetics? The specification seems to be referring to amino acid sequences in FR that are in human not other sources, however, the claims recite amino acids or amino acid residues. The response also did not address the phrase "primary design antibody" which is still indefinite because it is still unclear if the antibody is humanized or if the method starts with an un humanized antibody. In addition, it is still unclear how the homology search is carried out. Is the search between a human antibody and the humanized "primary design" antibody or between a human antibody and the humanized antibody?

The Following are Some NEW GROUNDS of Rejection

Claim Rejections - 35 USC § 112

12. Claims 14 and 3-5 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claims 14 and 3-5 are indefinite for reciting "high homology" in claim 14 because the exact meaning of the phrase is not clear. It is unclear what the criteria is for "high homology". Is it 80%, 90%, 99%?

b. Claims 14 and 3-5 are indefinite for reciting step (3) in claim 14 because the exact meaning of the phrase is unclear. Claim 14 part (3) recites preparing a list of amino acid sequences but does not state how or by what method they are prepared by. Is the step dependent on step (2)?

c. claims 14 and 3-5 are indefinite for reciting "contains a sequence that matches amino acids sequences substituted in step (10" in claim 14 because the exact meaning of the phrase is not clear. Does the sequence have to match the entire length of the FR region or only part or only those substitutions in part (1)?

Claim Rejections - 35 USC § 103

13. Claims 3-5 and newly added claim 14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sato et al (Molecular Immunology 31:371-381, 1994, IDS #4) and further in view of Queen et al (PNAS 86:10029-10033, 1989, IDS #4).

The claims recite a method of preparing a humanized antibody comprising obtaining a primary design antibody and conducting a homology search and preparing a list of amino acid sequences with high homology with FR sequences in the primary design antibody and selecting a sequence that matches the amino acid sequences

substituted in step 1 and replacing the different amino acids in the FR of the primary antibody with those in the natural FR and expressing and producing the antibody. Further claimed is a primary designed antibody comprises CDRs from a rat and the second species is a human.

Sato et al teach a method for humanization comprising CDR grafting by a homology search between the mouse antibody and human FR regions and selecting the most homologous and then comparing the resulting designed antibody to the consensus sequences for a subgroup to identify any highly irregular sequences (see entire document, especially page 380, right column). Sato et al do not teach a rat species. This deficiency is made up for in the teachings of Queen et al.

Queen et al teach a method of humanization comprising CDR grafting and homology searching and replacing FR residues and the species mouse and rat (see entire document, especially page 10029, right column, first full paragraph).

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have used the a rat antibody for humanization as taught by Queen et al in the methods of Sato et al.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have used the a rat antibody for humanization as taught by Queen et al in the methods of Sato et al because Queen et al teach that one can use either a mouse or a rat antibody for humanization. Moreover, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have used the a rat antibody for humanization as taught by Queen et al in

the methods of Sato et al because it was routine in the art at the time the claimed invention was made to use mouse as well as rat and other non-human a species as the antibody to humanize. Although Sato et al does not specifically recite the steps of the claimed method in claim 14 it would have been obvious to conduct a homology search using a data base of FR of human antibodies and prepare a list of sequences because Sata et al teach designing based on consensus sequences from individual antibodies and the consensus sequences will filter out any unusual and possibly more immunogenic sequences peculiar to an individual human antibody (see page 380, left column). Thus, it would have been obvious to one of skill in the art to select FR that are more human like in order to reduce the immunogenicity and obviously those FR that are fully human would be less immunogenic in humans.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

14. Claims 3-5 and newly added claim 14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Co et al (PNAS 88:2869-2873, 1991, IDS #4) and further in view of Queen et al (PNAS 86:10029-10033, 1989, IDS #4).

The claims have been described supra.

Co et al teach a method for humanization comprising CDR grafting by a homology search between the mouse antibody and human FR regions and selecting the most homologous and then replacing mouse residues with human residues because of the mouse residues were rare in the human antibodies and this would eliminate the

unusual amino acids in the FR which may further reduce immunogenicity (see entire document, especially page 2871, right column).

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have used the a rat antibody for humanization as taught by Queen et al in the methods of Co et al.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have used the a rat antibody for humanization as taught by Queen et al in the methods of Co et al because Queen et al teach that one can use either a mouse or a rat antibody for humanization. Moreover, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have used the a rat antibody for humanization as taught by Queen et al in the methods of Co et al because it was routine in the art at the time the claimed invention was made to use mouse as well as rat and other non-human a species as the antibody to humanize. Although Co et al does not specifically recite the steps of the claimed method in claim 14 it would have been obvious to conduct a homology search using a data base of FR of human antibodies because Co et al teach designing based on homology searches and in the Pom FR residues were substituted with consensus human residues because of the rare occurrence and this method eliminates the unusual amino acids in the FR which may further reduce immunogenicity (see page 2871, right column). Thus, it would have been obvious to one of skill in the art to select FR that are more human like in order to reduce the immunogenicity and obviously those FR that are fully human would be less immunogenic in humans.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

15. Claims 1-5 are rejected under 35 U.S.C. 103(a) as being unpatentable over Roguska et al (Protein Engineering 9:895-904, 1996, IDS #3) as applied to claims 1-3 and 5 above, and further in view of Queen et al (PNAS 86:10029-10033, 1989, IDS #4).

The claims have been described supra.

Roguska et al teach a method of humanization comprising CDR grafting by a homology search between the mouse antibody and human FR regions and selecting the most homologous and then replacing residues in the antibody with those found in the human FR (see page 898, left column, GN901v1.1).

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have used the a rat antibody for humanization as taught by Queen et al in the methods of Roguska et al.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have used the a rat antibody for humanization as taught by Queen et al in the methods of Roguska et al because Queen et al teach that one can use either a mouse or a rat antibody for humanization. Moreover, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have used the a rat antibody for humanization as taught by Queen et al in the methods of Roguska et al because it was routine in the art at the time the claimed

invention was made to use mouse as well as rat and other non-human a species as the antibody to humanize. Although Roguska et al does not specifically recite the steps of the claimed method in claim 14 it would have been obvious to conduct a homology search using a data base of FR of human antibodies because Roguska et al teach designing based on homology searches of human FR sequences and comparing those residues that are found in the mouse FR with those found at that position in human FR sequences and replacing mouse residues with human to obtain an antibody that are no more likely to be immunogenic that a corresponding CDR-grafted version (see page 901, right column). Thus, it would have been obvious to one of skill in the art to select FR that are more human like in order to reduce the immunogenicity and obviously those FR that are fully human would be less immunogenic in humans.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Conclusion

16. No claim is allowed.

17. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within

TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Larry R. Helms, Ph.D, whose telephone number is (703) 306-5879. The examiner can normally be reached on Monday through Friday from 7:00 am to 4:30 pm, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

19. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 308-4242.

Respectfully,

Larry R. Helms Ph.D.

703-306-5879

Sheela Huff

SHEELA HUFF
PRIMARY EXAMINER